Applicants confirm the prior election to prosecute the invention of Group I. Claims 14-21 have been cancelled in view of the restriction requirement, solely in view of the restriction and to minimize excess claim fees, and without prejudice as to the pursuit of these claims in another co-pending application. The applicants reserve the right to traverse the restriction of claims 14-21 into two distinct Groups at that time.

II. Status of the claims

The applicants acknowledge with thanks the summary provided at the beginning of the Office action. As the prior examiner's amendments were not entered, the claims examined are understood to be the claims as amended in April, 2002.

Claim amendments generally adopt the examiner's suggestions and are discussed in greater detail below. No amendment is intended to be narrowing or to be made in acquiescence to any rejection. No new matter has been added by way of these amendments.

Claims 1-11, 14-21, 37 and 38 were pending in the instant application prior to entry of this amendment, and claims 1-11, and 37-48 are pending following such entry. A marked up copy of the amended claims and a copy of the pending claims following entry of the amendment herein are appended hereto.

III. The Definiteness of the Pending Claims

A The rejection of claims 1-11 should be withdrawn.

In paragraph 13(a) of the Office action, the Examiner alleged that claims 1-11 were indefinite "for the recitation 'in a manner that reduces ligand-mediated signaling' because 'reduces' is a comparative term but it is unclear to what the signaling is being compared." The examiner kindly suggested an amendment to clarify comparison "to a wild-type allele." (Office action at p. 4.)

The applicants have adopted the examiner's suggestion to state explicitly what was already implicit in the claim. (See, e.g., specification at pp. 9-10.) The applicants also appreciate that the present examiner agrees that "wild-type" is a word well suited to describe the reference sequence to be used. The prior examiner

had objected to this term on grounds of alleged indefiniteness. The applicants responded to this objection by explaining that the term "wild-type" refers to a non-mutant sequence of VEGFR-3. An exemplary sequence is provided in SEQ ID NO: 1 (see p. 21, lines 21-23), and dependent claims have been added to explicitly refer to that sequence. (See claims 45-47.) One dictionary definition of the term "wild type" - quoted in an earlier amendment - states that this term refers to "...gene ...of the type predominating in the wild population." (Glossary of Genetics and Cytogenetics, Reiger et al., Eds., Springer-Verlag, Publ., p. 568, 1976). Applicants agree that this term is clear to one of skill in the art and well suited for use in defining the invention as it relates to screening for mutations.

B. The rejection of claim 2 should be withdrawn.

In paragraph 13(b) the examiner alleged, "Claim 2 is indefinite for the recitation 'assaying for a mutation' because it is unclear whether the assaying detects a mutation. It is suggested that the claim be amended to clarify e.g., replace 'assaying for' with 'identifying'." The applicants respectfully traverse.

The allegations against claim 2 amount to nothing more than an observation concerning claim breadth (e.g., that the *claim does not require identification* of a mutation), and not a ground for indefiniteness. Independent claim 1 (from which claim 2 depends) similarly recites "assaying" and also recites the proper correlation depending on whether a mutation is present (and thus identified by the assaying) or absent (and thus not identified). Claim 2, which depends from claim 1, further limits the type of mutation for which to assay, but is not limited to assaying wherein the mutation is identified. (The method of the invention provides valuable information to a test subject *whether or not* the test subject actually has a mutation.) As set forth in parent claim 1, the *absence of the mutation* recited in claim 2 *correlates with no increased risk* according to the method of the invention. (The examiner acknowledges this perfectly understandable interpretation in the rejection and also when discussing the Ferrell et al. paper in paragraph 15 of the office action.)

Because the meaning and breadth of "assaying for a mutation" is clear, the rejection of claim 2 should be withdrawn. However, the applicants appreciate the

examiner's suggestion to have a claim that recites "identifying" and have added new, dependent claims to this effect. (See claims 39-44.)

C. The rejection of claims 3-4 should be withdrawn.

In paragraph 13(c) the examiner made an analogous rejection of claims 3 and 4, for reciting "assaying". This rejection should be withdrawn for reasons set forth above.

The examiner also alleged that "corresponding" in claims 3 and 4 was indefinite "because 'corresponding' is a nonspecific relational phase." The applicants agree that "corresponding" expresses a relationship, but dispute the allegation that it is indefinite. One of ordinary skill in the field would have no difficulty discerning what portion of a particular person's VEGFR-3 sequence corresponded to the particular codons recited in the claim.

For example, at the time that the application was filed, numerous computer programs had been developed that performed complex DNA or protein sequence comparison and alignment of two or more sequences having sequence similarity. The literature in the field provides ample evidence of this, as it is quite commonplace to find articles and patents containing figures aligning similar, but non-identical, gene sequences obtained from multiple species. Using such alignments, one of ordinary skill can usually determine which codon in the gene of one species corresponds with a particular codon from another.

The claims at issue recite the comparatively simple task of comparing a nucleic acid/encoded protein sequence of *one human* with a *reference human sequence* in SEQ ID NO:1. Given the near perfect gene sequence identity shared by most members within any mammalian species, a person skilled in the art could reasonably be expected to perform the sequence relationship analysis involved in claims 3 and 4, to determine codon correspondence, by hand, without any need for computers. One certainly could perform such comparisons with computer software used in the field at the time that the application was filed.

Because one of ordinary skill would have no trouble whatsoever assaying a human subject's DNA for a mutation at a position corresponding to the

particular reference sequence recited in claims 3 and 4, the rejection should be withdrawn.

IV. The Novelty and Nonobviousness of the Pending Claims

Claims 1-4, 6-10, and 37-38 stand rejected under 35 U.S.C. §102(a) as being anticipated by Ferrell *et al.* (*Human Molecular Genetics, 7(13):* 2073-2078 (1998); hereafter "Ferrell *et al.*"). Claim 11 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Ferrell *et al.*, and claim 5 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Ferrell *et al.* in view of Lawrence *et al.* (*American Journal of Human Genetics, 63(4)*, Abstract 1053, A185 (1998); hereafter "Lawrence *et al.*") and Kimak *et al.* (*American Journal of Human Genetics, 63(4)*, Abstract 180, A185 (1998); hereafter "Kimak *et al.*").

All of the prior art rejections rely in whole or in part on Ferrell *et al.*, a publication authored in part by two of the named inventors on the application. It is axiomatic that an inventor's own work cannot be applied against the inventor as prior art under 35 USC §102(a) or §103, absent a statutory bar situation.

A "Declaration Under 37 C.F.R. § 1.132 of Dr. Robert Ferrell" (hereafter "Ferrell Declaration") filed herewith, establishes that, to the extent the Ferrell *et al.* publication discloses or suggests aspects of subject matter being claimed, such disclosure or suggestion is the work of co-applicants Ferrell and Finegold. In fact, to the extent Ferrell *et al.* discloses or suggests a complete invention of any particular claim, it is an invention of Ferrell and Finegold.

However, Ferrell *et al.* does not, in fact, disclose or suggest all aspects of the present invention. For example, there is no disclosure of functional effects of Flt4 mutations reported in the paper. As Dr. Ferrell states in the Declaration filed herewith, characterization of such function was a contribution that came from co-inventors Alitalo and Karkkainen. To the extent that one or more claims embody this

aspect of the invention, such claims are neither anticipated nor rendered obvious by Ferrell *et al.*, alone or in combination with any other reference.[1]

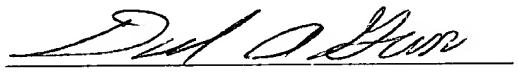
For the foregoing reasons, the rejections based on prior art should be withdrawn.

CONCLUSION

In light of the foregoing amendments and remarks, it is submitted that all claims are in condition for allowance. Should the Examiner wish to discuss any further material of form or substance, she is encouraged to contact the undersigned agent at the telephone number listed below.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By: 

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February 5, 2003

[1] Attached hereto as Exhibits 1-3 are additional articles, published after the filing date, by co-inventors Alitalo and Karkkainen. Both articles pertain to VEGFR-3 mutations and lymphedema. The *Nature Genetics* and *PNAS* articles also list co-inventors Ferrell and Finegold as authors.

VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

1. (Three times amended) A method of assaying for risk of developing hereditary lymphedema, comprising assaying nucleic acid of a human subject for a mutation that alters [altering] the encoded amino acid sequence of at least one VEGFR-3 allele of the human subject [in a manner that] and reduces ligand-mediated signaling of the VEGFR-3 polypeptide encoded by the allele, when compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele;

and correlating presence or absence of said mutation in the nucleic acid to a risk of developing hereditary lymphedema, wherein presence of said mutation in the nucleic acid correlates with an increased risk of developing hereditary lymphedema, and wherein absence of said mutation in the nucleic acid correlates with no increased risk of developing hereditary lymphedema.

7. (Twice amended) A method of screening for a VEGFR-3 hereditary lymphedema genotype in a human subject, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from said subject, said nucleic acid including sequences corresponding to said subject's VEGFR-3 alleles;

(b) determining a VEGFR-3 genotype by analyzing said nucleic acid for the presence of a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele, wherein the presence of a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele of the human subject in a manner that reduces signaling of the VEGFR-3 polypeptide encoded by the allele, when compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele, identifies a hereditary lymphedema genotype.

38. (Amended) The method of claim 37, wherein said mutation reduces signaling of the VEGFR-3 receptor compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele.